REMARKS

The Advisory Action mailed October 4, 2005 states that the claim amendments submitted with the response filed September 8, 2005 would not be entered; thus, the preceding amendments are based on the claims pending when the March 8, 2005 Office Action was issued.

Claims 1, 4, 7, 9, 10, 12, 13-16 and 18 are amended and claims 48-50 are added. The amendments are made without prejudice and without acquiescing to any of the Examiner's objections. Applicant reserves the right to pursue any canceled subject matter in a further application with the same rights of priority as the instant application.

Claim 1 is amended to recite a full-length chymosin pro-peptide and to clarify that the aspartic protease is capable of cleaving the pro-peptide from the fusion protein to release the recombinant polypeptide. Claims 12 and 18 are revised to recite more clearly the embodiment where step c) is effected in vivo, in the milk, stomach or gut of an animal. Claims 48 and 49 are added to recite the embodiment where step c) is effected in vivo by expressing the aspartic protease in the host cell. Claim 50 is added to recite the embodiment where the aspartic protease of step c) is pepsin. The other claims are amended to make clerical changes that do not affect the scope of the claims.

These amendments are fully supported by the specification as filed. For example, the amendments to claim 1 are supported at page 11, lines 24-25 (disclosing the use of a full-length pro-peptide sequence) and page 5, lines 17-18 (disclosing that the pro-peptide is cleaved from the fusion protein to release the recombinant polypeptide). New claims 48 and 49 are supported in the paragraph bridging pages 12 and 13. New claim 50 is supported at page 12, lines 27-28.

The substantive amendments were discussed during the Examiner Interview held on July 28, 2005, and are believed to place the application in condition for allowance, as explained in the response filed September 8, 2005, and as shown below. Upon entry of

the amendments, claims 1, 4-10, 12-16, 18-19 and 48-50 will be pending. Applicant respectfully requests reconsideration of these claims in view of the following remarks.

Advisory Action

The Advisory Action states that the amendments submitted with the response filed September 8, 2005, would not be entered because the recitation of a nucleic acid sequence encoding a full-length chymosin pro-peptide would require a new search. This issue is mooted by the filing of an RCE.

The Advisory Action also states that the amendment to part c) of claim 1 to recite that the autocatalytically maturing aspartic protease is capable of "accurately" cleaving the chymosin pro-peptide appears to raise new matter issues. Applicant respectfully disagrees. As explained in more detail below, the specification as filed fully satisfies the written description requirement with respect to accurate cleavage of the pro-peptide. Nevertheless, in order to expedite prosecution, the instant amendments do not add the term "accurately" to claim 1.

Other than the amendments to part c) of claim 1, the instant amendments are identical to those presented with the response filed September 8, 2005. Thus, the arguments presented with that response apply with equal force to the instant claims.

March 8, 2005 Office Action

The March 8th Office Action included objections to the claims and rejections under §112, §102 and §103. The objections to the claims and the §112 and §102 rejections are fully addressed in the response filed September 8, 2005, and Applicant respectfully requests that the Examiner consider those arguments after entry of the instant claim amendments. The §103 Rejections are addressed again below, to clarify Applicant's position in view of the current amendments to claim 1.

§103 Rejections

Claims 1, 4, 6-9, 13, 15 and 19 were rejected under §103 as allegedly obvious in view of Ward and McCaman. Claim 5 was rejected as being obvious in view of Ward, McCaman and Fine or Walsh and Fine. Claim 14 was rejected over Walsh and Dunn or Ward, McCaman, and Dunn. Applicant respectfully traverses these rejections.

Claims 1, 4, 6-9, 13, 15 and 19 (Ward & McCaman)

The combination of Ward and McCaman does not teach or suggest the invention recited in claims 1, 4, 6-9, 13, 15 and 19, as shown below.

Ward is cited for teaching a nucleic acid encoding a fusion protein that includes a bovine chymosin prosequence as a cleavable linker. As recognized by the Examiner, Ward does not teach or suggest the use of mature chymosin or any other mature form of an autocatalytically maturing aspartic protease to cleave the chymosin prosequence from the fusion protein. Indeed, Ward does not provide any specific teachings of how to cleave the bovine chymosin prosequence from its fusion protein. Instead, Ward states that "[t]he cleavable linker may then be cleaved using techniques known in the art." Ward, col. 14, lines 28-31.

The Office Action does not cite and Applicant is unaware of any prior-art reference that suggests the use of a mature form of an autocatalytically maturing aspartic protease, such as mature chymosin, to cleave a chymosin pro-peptide from a fusion protein, as presently recited. Accordingly, the obviousness rejection is improperly founded on hindsight and should be withdrawn.

Although this rejection also relies on McCaman, that reference does not teach or suggest the use of a mature aspartic protease to cleave a chymosin pro-peptide from a fusion protein. McCaman relates to the autocatalytic activity of aspartic proteases, and in no way teaches or suggests the use of mature aspartic proteases to cleave an aspartic protease pro-peptide sequence, such as a chymosin pro-peptide sequence, from a fusion protein, as presently claimed. It is only Applicant who recognized the

usefulness of mature aspartic proteases in that context, as the present specification amply discloses.

Applicant has explained before that, prior to the present invention, those skilled in the art had no expectation that a mature aspartic protease would be capable of cleaving a chymosin pro-peptide sequence from a fusion protein to release a recombinant polypeptide of interest. There was uncertainty as to whether a mature aspartic protease would release an intact recombinant polypeptide (i.e., whether the recombinant polypeptide would be cleaved at other sites) and as to whether a mature aspartic protease would precisely cleave the pro-peptide from the fusion protein (i.e., whether cleavage would result in undesired overhangs). The accurate cleavage reported in the specification (see, e.g., Examples 1 and 2) was therefore surprising and unexpected, and satisfies a long-felt need in the art for a method of cleaving fusion proteins to release a recombinant protein of interest.

The general uncertainty surrounding the ability to cleave a cleavable linker from a fusion protein to obtain a polypeptide of interest is reflected in Ward itself. For example, column 14 notes that "[i]n some embodiments, after cleavage . . . the desired polypeptides contain unwanted amino acids" that can be removed using "aminopeptidases and carboxypeptidases of differing specificities." These teachings further demonstrate that Ward does not teach or suggest a method as claimed, i.e., a method using a mature form of an aspartic protease that is capable of cleaving a chymosin pro-peptide from a fusion protein to release a recombinant polypeptide of interest. Thus, the combination of Ward and McCaman does not teach or suggest the present invention.

Although the Advisory Action alleged that the addition of the term "accurately" to claim 1 might raise new matter issues, inasmuch as claim 1 is not limited to the specific examples where accurate cleavage was demonstrated, Applicant emphasizes that the ability of the present invention to achieve accurate cleavage of the pro-peptide to release the recombinant polypeptide of interest is supported throughout the

specification as filed, and embodied in the instant claim language. For example, page 4, lines 12-13, and page 5, lines 17-18, teach that the invention provides a method wherein the pro-peptide is cleaved from the fusion protein "to release the recombinant polypeptide." Page 12, lines 3-10, teach that a chymosin pro-peptide—hirudin fusion protein was prepared, and that the hirudin protein was "efficiently cleaved" from the pro-peptide in accordance with the invention, and Examples 1 and 2 demonstrate accurate cleavage of the pro-peptide and release of the recombinant polypeptide of interest. The concept of accurate cleavage is further conveyed by the discussion at page 13, describing embodiments where the recombinant polypeptide has therapeutic or nutritional activity that is inactive when the recombinant polypeptide is a part of the fusion protein, but active once the pro-peptide is cleaved in accordance with the invention. The concept of accurate cleavage also is embodied in the disclosure at page 14 of the usefulness of the present invention to purify recombinant proteins. As noted at page 14, lines 21-22, the pro-peptide cleavage reaction permits isolation of the recombinant protein of interest. Thus, the specification as filed plainly conveys to the skilled artisan that Applicant's possessed the embodiment of the invention where the pro-peptide is "accurately" cleaved from the fusion protein to release the recombinant polypeptide.

While instant claim 1 does not expressly recite the term "accurately," Applicant believes that the accuracy of the recited cleavage is reflected in claim language stating that "said chymosin pro-peptide is cleaved from said fusion protein to release said recombinant polypeptide" (emphasis added).

Claim 5 (Ward, McCaman & Fine or Walsh & Fine)

Claim 5 recites specific embodiments of the invention where the recombinant polypeptide is hirudin or carp growth hormone. The combinations of Ward, McCaman and Fine or Walsh and Fine do not teach or suggest this invention.

The teachings of Ward and McCaman and of Walsh, and their failure to teach or suggest the invention of claim 1, are discussed above and in the September response.

Fine is cited for teaching the recombinant expression of carp growth hormone. Fine's teachings, however, do not remedy the inability of Ward and McCaman or Walsh to have suggested the claimed method. Thus, the rejections of claim 5 over Ward, McCaman and Fine and Walsh and Fine should be withdrawn.

Claim 14 (Walsh & Dunn or Ward, McCaman, & Dunn)

Claim 14 recites specific embodiments of the invention where the aspartic protease is heterologous to the chymosin pro-peptide. The combinations of Walsh and Dunn or Ward, McCaman and Dunn do not teach or suggest this invention.

The teachings of Walsh, Ward and McCaman, and their failure to teach or suggest the invention of claim 1, are discussed in the September response and above. Dunn is cited for teaching that a number of aspartic proteases have the ability to proteolytically cleave a recognition site having Phe in the P1 position. However, the teachings of Dunn (and other references cited in the Office Action) relating to the ability of mature aspartic proteases to cleave specific peptides at specific sites in no way teaches or suggests the invention recited in claim 14, which recites a method wherein a mature aspartic protease other than chymosin is contacted with a fusion protein comprising a chymosin pro-peptide sequence and cleaves the chymosin pro-peptide from the fusion protein to release a recombinant polypeptide of interest.

As stated above, there simply is no hint in the prior art of using a mature aspartic protease to cleave a chymosin pro-peptide sequence from a fusion protein to release a recombinant polypeptide of interest. The fact that mature aspartic proteases have been shown to cleave specific peptides at specific sites in no way implicates the use of a mature aspartic protease in accordance with the present invention. As noted above, those skilled in the art had no reasonable basis for expecting that an aspartic protease would be capable of cleaving a chymosin pro-peptide from a fusion protein to release the recombinant polypeptide, and did not know, for example, whether the aspartic protease would cleave the recombinant polypeptide at undesired sites and/or would cleave off too many or too few amino acid residues around the junction between the

pro-peptide and the recombinant polypeptide. Without an assurance of accurate cleavage, there was no motivation to have employed an aspartic protease as presently claimed.

Because it is only the instant specification that recognizes and teaches that aspartic proteases are capable of cleaving a chymosin pro-peptide from a fusion protein to release a recombinant polypeptide of interest, this obviousness rejection is improperly founded on hindsight, and should be withdrawn.

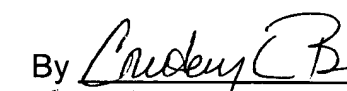
CONCLUSION

In view of the foregoing, we submit that the application is in order for allowance and an early indication to that effect would be greatly appreciated. Should the Examiner like to discuss the matter, he is kindly requested to contact Courtenay Brinckerhoff at 202 295 4094 or Micheline Gravelle at 416 957 1682.

The Commissioner is hereby authorized to charge any deficiency in fees (including any claim fees) or credit any overpayment to Deposit Account No. 02-2095.

Respectfully submitted,

BERESKIN & PARR

By 
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